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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/529,537	06/19/2000	LESLIE LARS IVERSEN	P24.002USA	9631

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EXAMINER	
CHOI, FRANK I	
ART UNIT	**PAPER NUMBER**
1616	

DATE MAILED: 04/19/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/529,537	IVERSEN, LESLIE LARS	
	Examiner	Art Unit	
	Frank I. Choi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 21-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 21-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Specification

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper (See Specification at pages 5-7). Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 179 USPQ 167 (CCPA 1973). The claims are directed to CCK antagonists, as such, the description of CCK antagonists in the Specification constitutes essential material.

Notwithstanding the fact that Applicant discloses other CCK antagonists, the fact remains that Applicant has attempted to incorporate by reference the CCK antagonists, which Applicant acknowledges as being essential material, disclosed in several European patent documents and the J. Med. Chem. 34 1508 (1991). Examiner notes that the formulas on pg. 6 are incomplete as they contain undefined variables, as such, it is impossible to tell from reading the Specification what compounds would and would not fall within the scope of said formulas. Said variables are presumedly defined in the foreign references EP 167 919, 284 256 and 405 537, and the cited publication, however, said definitions cannot be incorporated by reference to the same. For the same reasons, it is impermissible to incorporated by reference the preferred CCK antagonists disclosed in the European Patent specifications nos. 508 796, 652 871, 411 668, 421 802 and 617 621. Therefore, the only properly disclosed examples of CCK antagonists are those of formula

(I) and the specifically named CCK antagonists listed on pg. 6, lines 5-6 and Pg. 7, lines 1-10). See MPEP 608.01(p) [R-2] (I).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 21-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 1 564 039 in view of Woodruff et al., Patel et al., Ecanow (US Pat. 4,963,367), EP 0 391 369 and Dappen et al. (U.S. Pat. 5,223,507) for the reasons of record and the further reasons below.

GB 1 594 039 teaches the combination of alpha-d-propoxyphene and codeine with benzodiazepines, such as medazepam, and that the benzodiazepines enhanced the analgesic activity (See entire document, especially pgs. 2,3, Pg. 4, lines 1-26)). It is disclosed that propoxyphene is structurally related to methadone and that the alpha-dextro isomer is as effective in humans as codeine in relieving pain (Pg. 1, lines 10-36). It is disclosed that combination of diazepam and/or chlodiazepoxide to alpha,dextro-propoxyphene even at doses below those at which these benzodiazepines exhibit tranquilizing effects resulted in improved analgesia (Pg. 1, lines 65-74). It is disclosed that the compositions can be any of the normal oral forms, including tablets, capsules and suspensions or intravenously (Pg. 3, lines 88-108).

Woodruff et al. teach that that benzodiazepines, including flurazepam, diazepam, lorazepam, chlordiazepoxide, medazepm, devazepide, L-356260, L-365031, are CCK antagonists (Pgs. 480-484). It is disclosed that CCK acts as an opiate antagonist and that CCK

antagonists can potentiate the effects of analgesics of the morphine type while protecting against the development of narcotic tolerance and may be clinically useful in management of chronic pain (pgs. 487, 489).

Patel et al. teach that CCK antagonists, such as devazepide, are poorly water soluble (Pg. 947).

Ecanow disclose a two phase composition for parenteral and oral administration of water-soluble and water-insoluble or oil-soluble drugs in which one phase is colloid-rich and semipolar to nonpolar in character and capable of solubilizing oil-soluble and water-insoluble components and thee second phase is colloid-poor and semiploar to polar and capable of solubilizing water-soluble and to a lesser degree, water-insoluble compositions (Column 7, lines 25-63). It is disclosed that the drugs include codeine,diazepam, fentanyl, morphine, naloxone (Column 9, lines 32, 47, Column 10, lines 5,63,65, Column 12, lines 56, 67). It is disclosed that once the drug is solubilized in the colloid-rich phase, the colloid-poor phase can be added, which can be used to solubilize and prepare formulations of polar and semipolar drug compositions, and a microemulsion formed followed by adjustment of the pH adjusted, if necessary, for example to 7.3-7.4 by HCL or sodium bicarbonate (Column 13, lines 11-30). It is disclosed that the composition can be dried and that when reconstituted for intravenous use, isotonicity and pH should be adjusted by known procedures to normal body values before administration (Column 16, lines 48-63). It is disclosed that for parenteral administration its preferred that the microparticles of the finished products of the invention be 1 micron or less (Column 17, lines 3-6). It is disclosed that for oral composition, composition which have solvent properties but

which also serve as a matrix or substrate of the incorporated drugs include glycerides, such as mono,di and/or triglycerides (Column 15, lines 37-44).

EP 0 391 369 disclose that an oil-in-water emulsion in which the hydrophobic drug is dissolved in the oil phase which contains mid-chain triglycercides (MCT) or a mixture MCT and a conventional vegetable oil, such as soybean, cotton seed, olive or sesame oil (Pg. 3, Pg. 4, lines 1-8, 30-33). It is disclosed that oil-in-water emulsions are the only practical way by which hydrophobic drugs can be administered intravenously (Pg. 3, lines 20,21). It is disclosed that the preferred ph of the aqueous phase is about 5.0-8.5, while 6.0-8 being more preferred, especially for parenteral administration (Pg. 4, lines 28,29). It is disclosed that the compositions can be used for parenteral, oral or topical administration of the drug (Pg. 3, lines 32,33). It is disclosed that an osmotic pressure regulator such as glycerin or mannitol can be added (Pg. 4, lines 56-58). It is disclosed that the hydrophobic drugs include hydrophobic and lipophilic narcotic drugs such as alkaloid bases, such as morphine-base, and hydrophobic benzodiazepines, such as diazepam (Pg. 5, lines 3-6). It is disclosed that the oily droplets should preferably be small, i.e. below about 1 micron for purposes of stability and with respect to parenteral administration since large droplets will not readily pass through small blood capillaries (Pg. 5, lines 17-22)..

Dappen et al. teaches that gelatin, alginates, cross linked carboxy methyl cellulose and other celluloses, PVP, lactose and other non-toxic compatible substances are suitable excipients for pharmaceutical dosage forms containing opioids (Columns 25-29, Column 30, lines 1-36).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose the combination of opioid, CCK antagonist in a biphasic carrier. However, the prior art amply suggests the same as the prior art discloses the combination of

opioid and CCK antagonist, that CCK antagonists are poorly water soluble and that oil-in-water emulsions are suitable for administering both hydrophobic and water-soluble drugs both intravenously and orally. As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to modify the prior art so as to formulate a pharmaceutical formulation which conveniently in a single formulation is able to administer the combination of the hydrophobic CCK antagonists with the opioid, which combination is expected to potentiate the analgesic activity of the opioid.

Examiner has duly considered Applicant arguments but deems them unpersuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 231 USPQ 375 (Fed. Cir. 1986). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 208 USPQ 871 (CCPA 1981).

Applicant argues that the prior art does not disclose the use of an opioid-potentiating amount of a CCK antagonist. However, the prior art as indicated above clearly indicates that the benzodiazpines are opioid-potentiating CCK antagonists. Applicant provides no evidence that medazepem is not a suitable compound. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience

is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.").

Contrary to Applicant's arguments, GB 1 564 039 includes 3-substituted, 1,4 substituted benzodiazepines (Pg. 2, lines 26-79). The fact that there are embodiments which are not 3-substituted is insufficient to overcome the rejection. The limitation "opioid-potentiating CCK antagonists" does not exclude non-3-substituted, 1,4 substituted benzodiazepines. Applicant acknowledges that alpha, d-propoxyphene is an opioid and GB 1 564 039 discloses that the benzodiazpines potentiate that activity of alpha-d-propoxyphene and Woodruff et al. discloses that they are CCK antagonists.. As such, the benzodiazepines have opioid-potentiating activity and they are CCK antagonists, as such, they meet the limitation. With respect to the exemplary compounds, said limitation does not limit the compounds to 3-substituted, 1,4-substituted benzodiazipines. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 26 USPQ2d 1057 (Fed. Cir. 1993). Finally, Woodruff et al., as indicated above, further disclose that CCK antagonistic benzodiazepines, such as devazepide, potentiate the analgesic activity of opioids. As such, the prior art clearly discloses the combination of a 3-substituted, 1,4-substituted benzodiazepine with an opioid.

Applicant argues that the biphasic carrier is an important aspect because is provides the means by which water-soluble opioids and lipid-soluble CCK antagonists may be delivered simultaneously. However, Applicant has argued that this aspect is not critical in that "the present invention does not preclude having components (a) and (b) present in any combination in any phase of the carrier" (Remarks (12/17/2004), pg. 9). As indicated above, since the rejection

herein is based on a combination of references, there is no requirement that a biphasic carrier be disclosed in the primary reference.

With respect to Patel et al, obviously, Examiner cannot use Applicant's Specification as prior art unless Applicant acknowledges a disclosure in the Specification as being prior art. As such, Patel et al. is cited to show that CCK antagonists, such as devazepide, are poorly soluble. Applicant argues that EP'369 only discloses carrying hydrophobic drugs. However, as indicated above, for the same reasons that the primary reference is not required to disclose the use of emulsions, EP'369 is not required to disclose the carrying of hydrophilic drugs. Dappen et al. is not being cited for a teaching of how to formulate a composition containing a water-soluble opioid and lipophlic compound but to show that the excipients claimed are commonly used as carriers for opioids.

It is the teachings of Ecanow and Benita et al. which discloses methods of preparing oil-in-water formulations containing hydrophobic drugs and that triglycerides are suitable carriers for hydrophobic drugs and Ecanow discloses that the aqueous phase can be used as a carrier for water-soluble drugs. Further, Bentita et al. discloses that oil-in-water emulsions are the only practical way by which hydrophobic drugs can be administered intravenously. Finally, Ecanow and Benita et al. discloses that the two phase compositions can be formulated for intravenous and oral use. Thus, based on the teachings of Ecanow and Benita et al. it would have been well within the skill of one ordinary of skill in the art to incorporate a hydrophobic CCK antagonist into oil phase and a hydrophilic opioid into an aqueous phase and mix the two phases to form an oil in water emulsion. Further, one of ordinary skill in the art would have been motivated to formulate the combination of opioid and CCK antagonist as an oil-in-water composition with the

expectation that the CCK antagonist would potentiate the activity of the opioid, and that the oil-in-water composition would be able to carry both the hydrophobic CCK antagonist and opioid as a single formulation for intravenous or oral use.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Conclusion

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Gary Kunz, can be reached at 571-272-0887. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

FIC
4/15/05

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